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Chapter 9

Estimating Renal Function in Paraplegia

Jennifer Pai Lee

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1. Introduction

The National Kidney Disease Education Program recommends using either the Cockcroft–Gault creatinine clearance (CL_{CG}) or Modification of Diet in Renal Disease (MDRD) equation when determining dosages of drugs that are primarily eliminated by the kidneys [1]. Both methods attempt to better predict creatinine clearance (CL_{CR}) or glomerular filtration rate (GFR) by taking into account different variables such as age, weight, gender, race, and serum creatinine (SCr), however neither equation captures the key factor of paraplegia. Over time, individuals with paraplegia develop low SCr concentrations relative to their actual CL_{CR} due to significantly reduced muscle mass as a result of chronic immobility and muscle atrophy. Both Cockcroft–Gault (CG) and MDRD formulas have SCr in their denominator inversely proportional to CL_{CR} or GFR, therefore low SCr in paraplegia would result in gross overestimation of their renal function. Based on falsely high CL_{CR} or GFR, clinicians could potentially prescribe renally eliminated medications at dosages higher than recommended, resulting in undesirably high drug concentrations leading to drug toxicity and/or adverse drug reactions (ADRs). For example, supratherapeutic vancomycin and aminoglycosides (AG) serum concentrations, especially if combined with other nephrotoxic and/or ototoxic medications, could drastically increase the risk of nephrotoxicity and/or ototoxicity. This could be devastating to many individuals with paraplegia who have existing renal insufficiency.

In addition to high prevalence of traditional risk factors for CKD such as advanced age, diabetes, hypertension, and cardiovascular disease, individuals with paraplegia have elevated incidence of recurrent and chronic urinary tract infections, neurogenic bladder dysfunction, and nephrolithiasis that put them at risk for developing CKD [2-6]. Fischer et al. conducted cross-sectional analyses of data on 9333 Veterans with spinal cord injury and disorder (SCI/D) and found that the prevalence of CKD in SCI/D was approximately 35%, considerably higher based on the modified MDRD for SCI/D than 10% based on the original MDRD

formula [7]. Underrecognition of CKD in paraplegia makes it more crucial to use accurate tools to estimate renal function in this population.

Currently, there is no accepted standard method for determining renal dosing regimens for patients with paraplegia, and data on estimating renal function in such population is scarce. However clearance of drugs primarily eliminated by the kidneys such as vancomycin and AG nearly mirror that of the creatinine, hence could be used to assess renal function in paraplegia.

The aims of this chapter are: (1) to review the current literature on assessing renal function in paraplegia, (2) to evaluate different methods of estimating CL_{CR} or GFR compared with patient-specific vancomycin and AG clearance (CL_{DRUG}) in individuals with paraplegia, (3) to assess whether there is a difference in the estimation of renal function between the two anatomical degrees of SCI/D when compared with CL_{DRUG}, and (4) to present the "Spinal Cord Injury Equation" that more accurately estimates renal function in paraplegia.

2. Review of the current literature on assessing renal function in paraplegia

Tables 1 and 2 show, respectively, comparison of equations to predict CL_{CG} or GFR from SCr and review of the current literature on assessing renal function in paraplegia. Each equation and study will be discussed in detail below.

Equation 1: Cockcroft-Gault equation (CL_{CG}) [8]

GFR = CL_{CR} (mL/min) = [(140 – age) x IBW in kg] / (72 x SCr); (multiply 0.85 for females)

Equation 2: Modified Cockcroft-Gault equation (CL_M) [16]

GFR = CL_{CR} (mL/min) = [(140 – age) x IBW in kg] / (72 x SCr); (multiply 0.85 for females)

SCr rounded to 1 mg/dL for patients with SCr < 1 mg/dL while using the actual SCr for patients with SCr ≥ 1 mg/dL

Equation 3: MDRD equation [11-13*]

GFR (mL/min/1.73 m^2) = 175 x standardized $SCr^{-1.154}$ x $age^{-0.203}$ x 1.212 (if black) x 0.742 (if female)

Equation 4: CKD-EPI equation [14*]

GFR (mL/min/1.73 m^2) = 141 x min (SCr/κ, 1)$^{\alpha}$ x max (SCr/κ, 1)$^{-1.209}$ x 0.993^{Age} x 1.018 [if female] x 1.159 [if black]

where κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/κ or 1, & max indicates the maximum of SCr/κ or 1.

Equation 5: 24-Hour endogenous creatinine clearance (CL_{24H}) [8]

GFR = CL_{24H} (mL/min) = [urine creatinine x urine volume (mL)] / [SCr x time (hours) x 60]

*To enable the expression of comparisons among different methods in the same unit (mL/min), GFR values normalized to a BSA of 1.73 m^2 need to be converted to uncorrected values.

Table 1. Comparison of Equations to Predict Creatinine Clearance (CL_{CR}) or Glomerular Filtration Rate (GFR) from Serum Creatinine Concentration

Characteristics	Macdi-armid et al. (2000) [9]	Mirah-madi et al. (1983) [10]	Chikka-lingaiah et al. (2010) [15]	Lee and Dang (2011) [16]	Lavezo et al. (1995) [18]	Lee and Yang (2013) [19]
SCI/D:	36	58	116	141	14	87
Paraplegics (P)	25	22	64	52	--	54
Tetraplegics (T)	11	36	52	89	--	33
Non-SCI/D (control)	--	22	--	--	14	--
Age (yr.) (mean ± SD)	38 (24-68)	P: 48 ± 17 T: 47 ± 14	63 ± 1	66 ± 11	53 ± 12	65 ± 16
Male (n [%])	--	SCI/D: 58 [100] Control: 11 [50]		140 [99]		87 [100]
Race (n [%]) **White and other** **Black**	--	--			75 [65] 41 [35]	71 [82] 16 [18]
BMI (kg/m²) (mean ± SD)	--	--		25 ± 6		27 ± 5
CL_{CG} (mL/min) (mean [SD])		P: 82 ± 46 T: 70 ± 23		91 ± 37	63 ± 26	93 ± 47
MDRD GFR (mL/min/ 1.73 m²) (mean ± SD)	--	--			76 ± 33	
SCr (mg/dL) (mean ± SD)	--	P: 1 ± 0.4 T: 0.8 ± 0.3		0.74 ± 0.29	SCI/D: 0.8 ± 0.4 Control: 1.1 ± 0.3	0.88 ± 0.40
Methodology	CL_{CG} vs. CL_{24H} vs. measured CL_{CR} by ^{99m}Tc-DTPA	CL_{CG} vs. CL_{24H}	CL_{CG} vs. CL_{24H} vs. MDRD	CL_{CG} vs. CL_M vs. CL_{24H} vs. MDRD vs. CKD-EPI	SCI/D vs. Non-SCI/D CL_{VANCO}	CL_{SCI} vs. CL_{CG} vs. CL_M vs. CL_{24H} vs. MDRD vs. CKD-EPI
Findings/ Recommen-dations	CL_{24H} more accurate than CL_{CG}	Correction factor: 0.8 for paraplegic 0.6 for tetraple-gic	Correction factor: 0.7 for MDRD 0.8 for CL_{CG}	All methods over-estimate CL_{DRUG} ($P < 0.001$). Devel-opment of CL_{SCI}	↑half-life in SCI/D	Verifi-cation of CL_{SCI}: CL_{SCI} un-biased and more precise.

Table 2. Review of the Current Literature on Assessing Renal Function in Paraplegia

a. The Cockcroft-Gault (CG) equation (CL_{CG})

CL_{CG}(mL/min) = [(140 – age) x IBW in kg] / (72 x SCr);
(multiply 0.85 for females)

The CG equation was derived from a study of 236 males aged 18-92 years based on their 24-hour creatinine excretion. Since the publication in 1976, it has been exclusively used to estimate CL_{CR} based on SCr to calculate dosing regimens for renally cleared medications including vancomycin and AG. However it may not extrapolate to individuals with paraplegia because the CG study excluded 31 patients with 24-h creatinine excretion < 10 mg/kg, and it didn't reveal whether the study population included paraplegia and to what extent [8].

The review of current literature reports significant overestimation of renal function by CL_{CG}, thus does not recommend using the original equation in paraplegia [9-10].

Macdiarmid et al. studied 25 paraplegic and 11 tetraplegic patients and sought to compare their CL_{CG} and 24-hour endogenous creatinine clearance (CL_{24H}) to the measured CL_{CR} by ^{99m}Tc-DTPA clearance technique [9]. The investigators found that the CG method did not correlate well with that of the CL_{24H} (r=0.426) or ^{99m}Tc-DTPA clearance (r=0.366) [9]. The mean difference between CL_{CG} and CL_{24H} was 41.9%, and the difference between CL_{CG} and ^{99m}Tc-DTPA clearance 50.7% where CG formula overestimated CL_{CR} [9]. On the other hand, the difference between CL_{24H} and ^{99m}Tc-DTPA clearance was 17.7% with good correlation (r=0.71) [9]. The authors concluded that the CG formula significantly overestimates CL_{CR} thus not recommended, however CL_{24H} is an accurate method of determining renal function in paraplegia [9].

A study by Mirahmadi et al. investigated 58 male hospitalized patients with SCI/D and 22 ambulatory subjects, and compared their measured CL_{24H} by autoanalyzer method versus the predicted by CL_{CG} [10]. The authors found that the predicted CL_{CG} and measured CL_{24H} values closely matched in the ambulatory group while the predicted values consistently exceeded the measured values in SCI/D [10]. Between the two anatomical degrees of SCI/D, the paraplegic group had a markedly higher SCr (1.0 ± 0.4 mg/dL) and 24-hour urinary creatinine excretion (16 ± 9 mg/kg) compared to the tetraplegic group where the respective values were 0.8 ± 0.3 mg/dL and 11 ± 4.6 mg/kg [10]. The authors modified the original CG formula using a correction factor of 0.8 for paraplegics and 0.6 for tetraplegics to overcome significant overestimation by CL_{CG} [10]. The correction factors improved the accuracy and precision of the predicted CL_{CG} shown by the difference between the predicted and measured CL_{CR} approaching zero and the slope of a linear correlation between the predicted and measured values approaching one with decreased Y-intercept values ($p < 0.01$) [10].

b. The MDRD equation (MDRD)

4-Variable MDRD:

GFR (mL/min/1.73 m^2) = 175 x standardized $SCr^{-1.154}$ x $age^{-0.203}$ x 1.212 (if black) x 0.742 (if female)

A more recently developed MDRD has been widely used to estimate GFR in the nephrology arena. It is one of the two equations recommended by The National Kidney Disease Education Program for drug dosing [1].

The MDRD equation was derived from a study of a relatively young non- paraplegic population (mean age 51±13 years) with chronic kidney disease, primarily to stage kidney disease [11-12]. The original 6-variable MDRD formula integrates patient parameters including age, gender, race, blood urea nitrogen (BUN), SCr, and serum albumin [11-12]. The performance of this equation can be limited by variability among clinical laboratories in calibrating SCr assays [13]. Thus, the formula was re-expressed as the 4-variable MDRD equation based on standardized SCr assays as shown above [13]. Despite SCr calibration, the accuracy of the equation remains compromised at levels of GFR >60 mL/min/1.73 m^2 [12-14]. Nevertheless, MDRD stands useful for GFR <60 mL/min/1.73 m^2 in non- paraplegia and is endorsed by the National Kidney Disease Foundation for estimating GFR in CKD patients [1, 11-12].

Chikkalingaiah et al. compared the performance of the 4-variable MDRD and CG equations with CL_{24H} in 64 patients with chronic paraplegia of greater than 6 months duration and stages II-V CKD [15]. Precision and bias of MDRD and CG formulas were measured by combined root mean square error (CRMSE) calculated as the square root of [(mean difference of estimated GFR and measured CL_{24H})^2 + (SD of the difference)^2]. Respective CRMSE values for original MDRD and CG equations were 29 and 19.3 mL/min/1.73m^2. In order to improve the performance of the prediction equations, a correction factor of 0.7 for MDRD and 0.8 for CG were applied which resulted in a decrease in their CRMSE values to 11.4 and 13 mL/min/1.73m^2, respectively [15]. Accuracy of both prediction equations was evaluated by the percentage of patients who did not deviate >15%, 30%, or 50% from measured CL_{24H}. Respective percentages for MDRD were 12.5, 25, and 48.4 before the correction, and 25, 42, 68 after the correction [15]. Respective percentages for CG were 22, 37.5, and 58 before the correction, and 25, 50, 75 after the correction [15]. On the whole, the CG equation had less bias and was more precise and more accurate than the MDRD equation, however still overestimated GFR in subjects with chronic paraplegia with measured CL_{24H} < 90 mL/min/1.73m^2. Application of the correction factors markedly improved in the overall bias, precision, and accuracy of both MDRD and CG equations shown by both decreased CRMSE values and increased percentage of subjects in whom GFR did not deviate >15%, 30%, or 50% from measured CL_{24H} [15].

c. The CKD-EPI equation (CKD-EPI)

GFR (mL/min/1.73 m^2) = 141 x min (SCr/κ, 1)$^{\alpha}$ x max (SCr/κ, 1)$^{-1.209}$ x 0.993^{Age} x 1.018 [if female] x 1.159 [if black]

where κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/κ or 1, & max indicates the maximum of SCr/κ or 1.

In order to overcome the known bias of the MDRD equation for GFR values of ≥60 mL/min/1.73 m^2, the researchers pooled the data from 26 studies to develop and validate a new equation, the CKD-EPI equation, to define dose modification across the GFR range in patients with and without CKD [14]. The data showed that the CKD-EPI equation was more precise and accurate compared to MDRD, especially at GFR > 60 mL/min/1.73 m^2, however it is not frequently used

in current clinical practice when determining dosages of drugs that are primarily eliminated by the kidneys due to need for further validation. Furthermore, the sample population used to develop the CKD-EPI formula did not include paraplegia, thus its use in paraplegia may be misleading.

d. 24-Hour endogenous creatinine clearance (CL_{24H})

CL_{24H} (mL/min) = [urine creatinine x urine volume (mL)] / [SCr x time (hours) x 60]

Current literature reports that CL_{24H} better predicts renal function compared to CL_{CG} and MDRD in paraplegia, however this method is not routinely utilized for drug dosing due to the impracticability of collecting multiple urine samples as well as the propensity for error from serial collections [8, 16].

3. Evaluation of different methods of estimating CL_{CR} or GFR compared with patient-specific vancomycin and aminoglycoside (AG) clearance (CL_{DRUG}) in individuals with SCI/D

Data on the application of methods of estimating renal function compared with patient-specific CL_{DRUG} in paraplegia is scarce.

Lavezo et al. compared the pharmacokinetics of vancomycin in 14 SCI/D and 14 non-SCI/D control patients with their age, weight, pharmacokinetic parameters of total body clearance, volume of distribution, and mean predicted dosages matched. Demographic data between the groups differed only in mean SCr where the values were 0.8 ± 0.4 in the SCI/D group and 1.1 ± 0.3 in the able-bodied control group (p=0.04). The investigators obtained the pharmacokinetic parameters via two steady-state vancomycin serum concentrations by the Sawchuk and Zaske method [17] and found that compared to the control group, mean elimination rate constant was significantly smaller, therefore mean elimination half-life significantly longer in patients with SCI/D [18]. The authors concluded that patients with SCI/D may require longer dosing intervals of vancomycin compared to non-SCI/D [18].

In 2011, Lee and Dang published the results of a retrospective pharmacokinetic analysis of data on 141 patients with long-term SCI/D in the Veterans Affairs (VA) hospital with the largest inpatient SCI center in the VA system. The investigators evaluated frequently employed methods to estimate GFR (CL_{CG}, modified CG, $CL_{24H,}$ MDRD, and CKD-EPI) against patient-specific drug clearance of vancomycin and AG (CL_{DRUG}) [16]. Table 3 shows that all methods overestimate CL_{DRUG} ($p < 0.001$). The mean difference between CL_{DRUG} and MDRD is largest where overestimation by MDRD is more than two-fold. Almost 70% of the patients had overestimation of CL_{DRUG} by greater than 30 mL/min when using MDRD to predict empiric dosing for vancomycin and AG ($p < 0.001$) [16]. The authors modified the original CG equation by rounding SCr to 1 mg/dL for patients with SCr < 1 mg/dL while using the actual SCr for patients with SCr ≥ 1 mg/dL in attempts to account for low SCr in SCI/D and to overcome gross overestimation of renal function by CL_{CG} [16]. The investigators found that the modified CG

equation (CL_M) better estimated CL_{DRUG} in SCI/D, compared with other frequently employed methods for predicting GFR. The mean difference between CL_{DRUG} and CL_M was smallest among the equations evaluated where overestimation by CL_M was approximately 40%. Almost 65% of the patients had prediction of CL_{DRUG} within 30 mL/min when using CL_M to estimate empiric dosing for vancomycin and AG ($p < 0.001$) [16]. Despite pronounced improvement by modification of CG, overestimation may not be clinically acceptable.

(N=141)	Mean ± S.D. (mL/min)	Difference from CL_{DRUG} (mL/min)	P-Value
CL_{DRUG}	49.77 ± 19.97	0	--
MDRD	119.76 ± 61.49	69.99	<0.001
CKD-EPI	90.71 ± 27.44	40.94	<0.001
CL_{24H}	85.16 ± 33.88	35.39	<0.001
CL_{CG}	91.24 ± 36.90	41.47	<0.001
CL_M	69.38 ± 13.49	19.61	<0.001

Abbreviations: GFR, glomerular filtration rate; $CL_{DRUG,}$ actual drug clearance; MDRD, the Modification of Diet in Renal Disease equation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; CL_{24H}, 24-hour endogenous creatinine clearance; CL_{CG}, the Cockcroft-Gault formula; CL_M, modified Cockcroft-Gault formula; S.D., standard deviation. Published with permission of Lee [16].

Table 3. Evaluation of Different Methods to Estimate GFR

4. Estimation of renal function between the two anatomical degrees of SCI when compared with CL_{DRUG}

As previously mentioned, Mirahmadi et al. reported that both SCr and mean urinary creatinine excretion were markedly lower in paraplegics compared with ambulatory subjects [10]. The authors recommended an adjustment of the original CG equation by 20% for paraplegics to correct for reduction of muscle mass relative to the total body weight in such population [10].

Chikkalingaiah et al. found that both prediction equations (MDRD and CG) overestimated GFR in the paraplegic group with an overestimation by MDRD to a higher degree [15]. The fractional prediction error (FPE = (variable 1-variable 2) x 100/variable 1) for MDRD and CG were, respectively, 48.5% and 29.5% for paraplegic subjects, where an FPE greater than 20% was considered to be clinically unacceptable [15]. A correction factor of 0.7 for MDRD and 0.8 for CG proposed by the authors decreased the FPE to 3.9% and 3.6%, respectively, for the paraplegic group [15].

Lee and Dang sought to evaluate various methods to predict CL_{DRUG} for different anatomical degrees of SCI/D (Table 4) [16]. The mean difference between CL_{SCI} and CL_{DRUG} was not statistically significant when separated into paraplegia and tetraplegia [16]. Similar finding was noted for CL_M and CL_{24H} [16]. On the other hand, the mean differences between CL_{CG}, CKD-EPI, and MDRD and CL_{DRUG} were statistically significant between the two anatomical

degrees of SCI where tetraplegics had a gross overestimation of CL_{DRUG} compared with paraplegics [16]. The investigators stated that such difference may have risen from rounding SCr up to 1 mg/dL for patients with SCr < 1 mg/dL and using a ratio of urine creatinine to SCr done in CL_M and $CL_{24H,}$ respectively, contrary to using the actual SCr in the other equations [16].

Individuals with paraplegia have variable functionality and range of mobility and movement depending on the injury levels. Degree of paralysis of lower body and legs and upper body strength could affect muscle mass therefore potentially alter SCr and CL_{CR} or GFR. For example, one with high paraplegia (>T7) may have weaker upper body strength and balance compared to the one with low (T7-T12) paraplegia thus may have lower muscle mass and SCr resulting in a falsely low estimation of renal function compared to the low paraplegia. Unfortunately, there has yet been a study that assesses renal function between different anatomical levels or severity of injury in paraplegia.

	Mean Difference from CL_{DRUG} ± S.D. (mL/min)		**p-Value**
	Paraplegics (n = 52)	**Tetraplegics (n = 89)**	
CL_{SCI}	-3.11 ± 13.14	-5.39 ± 21.16	0.48
CL_M	21.04 ± 13.81	18.76 ± 22.26	0.5
CL_{24H}	32.60 ± 30.78	37.02 ± 35.29	0.45
CL_{CG}	27.26 ± 20.56	49.76 ± 38.55	<0.001
CKD-EPI	27.52 ± 25.50	48.77 ± 24.76	<0.001
MDRD	40.68 ± 40.71	50.64 ± 64.56	<0.001

Abbreviations: $CL_{DRUG,}$ actual drug clearance; SCI, spinal cord injury; $CL_{SCI,}$ spinal cord injury equation; CL_M, modified Cockcroft-Gault formula; CL_{24H}, 24-hour endogenous creatinine clearance; CL_{CG}, the Cockcroft-Gault formula; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; MDRD, the Modification of Diet in Renal Disease equation; S.D., standard deviation. Published with permission of Lee [16].

Table 4. Evaluation of Methods to Predict CL_{DRUG} for Different Anatomical Degrees of SCI/D

5. The "Spinal Cord Injury Equation" (CL_{SCI})

Gross overestimation of CL_{DRUG} by the frequently employed methods for estimating GFR prompted the authors Lee and Dang to develop an alternative method of estimating CL_{DRUG} in SCI/D, the "spinal cord injury equation" (henceforth referred to as the CL_{SCI} equation):

$$CL_{SCI}\ (mL/min) = 2.3 \times CL_M^{\ 0.7}$$

where CL_{SCI} and CL_M denote, respectively, clearance values determined via use of the CL_{SCI} equation and the CL_M formula [16]. The CL_{SCI} equation yields a value along the *line of best fit* (the straight trend line depicting the line of least variability in all points on a scatterplot of data derived by regression analysis of two variables) between CL_M and patient-specific vancomycin clearance (CL_V) values [16].

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Figures 1 and 2 depict, respectively, plots of actual drug clearance versus modified CG predicted drug clearance and linear regression plots of actual drug clearance versus predicted drug clearance using the CL_{SCI} equation [16]. The slope of a linear correlation between the predicted and measured CL_V values approach one, and the Y-intercept of a linear correlation between the predicted and measured CL_V values is minimum [16].

The CL_{SCI} equation was tested against other methods through a retrospective analysis of 87 hospitalized patients with long-term SCI/D [19]. The study population had similar baseline characteristics to the previous population by Lee and Dang, exclusively elderly, overweight, males with similar SCr. The authors used the Sheiner and Beal method [20] for determining predictive performance (precision and bias) to evaluate the predictive ability of the CL_{SCI} equation in estimating vancomycin clearance, relative to five alternative methods (CL_{CG}, modified CG, $CL_{24H,}$ MDRD, and CKD-EPI). Compared with other equations, the CL_{SCI} equation was found to be less biased and more precise, with the smallest calculated mean prediction error (ME) and square root of the mean squared prediction error (RMSE) values ($p < 0.005$) (Table 5) [19]. Predictive performance of the CL_{SCI} relative to each of the other five methods was measured by change in ME (relative bias between two methods) and change in MSE (relative precision) (Table 6). Negative values for changes in ME and MSE indicate an advantage favoring the comparator; a greater negative value signifies a greater magnitude of error. The five alternative equations significantly overestimated CL_V, by 45-92% ($p < 0.05$) (Table 7) [19]. The CL_{SCI} equation underestimated CL_V by approximately 6%, however not to a significant degree ($p = 0.06$) [19]. The results of their finding were consistent with the previous study by Lee and Dang.

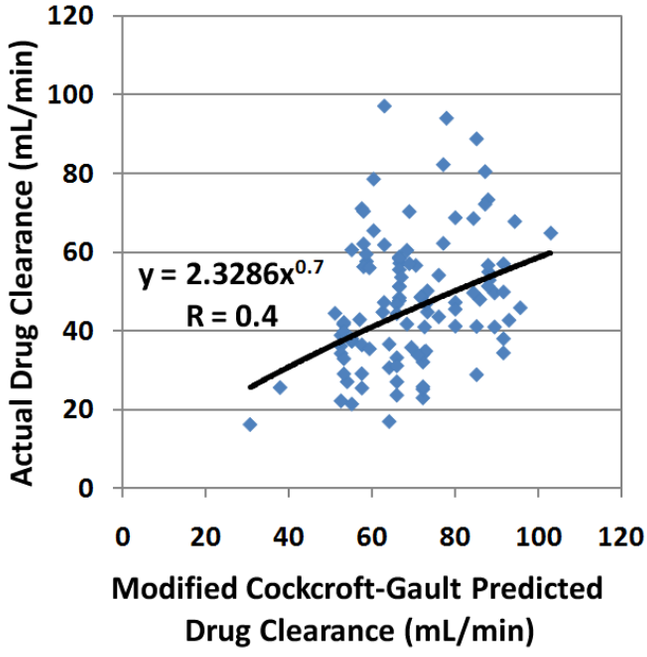

Figure 1. Plots of Actual Drug Clearance versus Modified Cockcroft–Gault Predicted Drug Clearance. Published with permission of Lee [16].

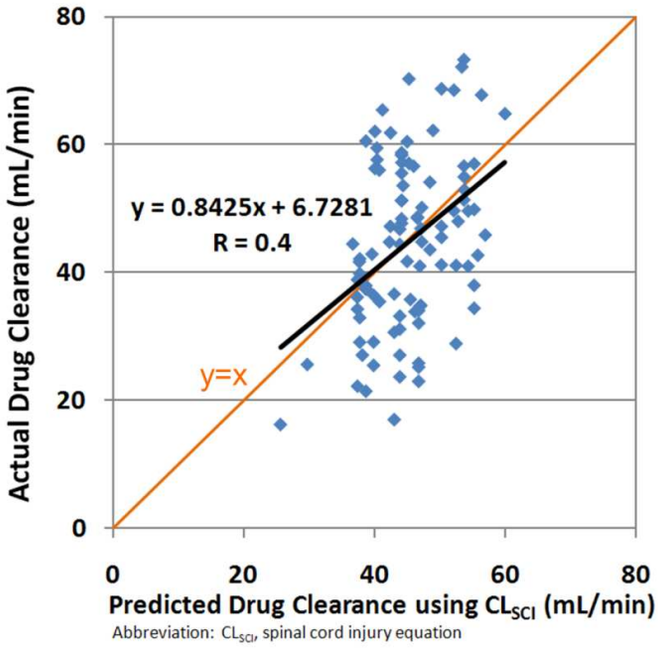

Figure 2. Linear Regression Plots of Actual Drug Clearance versus Predicted Drug Clearance Using the Spinal Cord Injury Equation. The red line, y=x, represents a line with a slope of 1 that indicates a perfectly one-to-one association between the actual and predicted drug clearance. Published with permission of Lee [16].

Parameter	CL_{SCI}	CL_M	CL_{24H}	CKD-EPI	CL_{CG}	MDRD
Bias						
ME (mL/min)	-3.1	21.5	32.5	33.0	44.5	47.5
95% CI (mL/min)	-6.3 to 0.1	17.8 to 25.1	26.2 to 38.8	27.7 to 38.4	36.2 to 52.7	31.2 to 55.8
Precision						
MSE (mL^2/min^2)	235.2	748.9	1925.2	1712.7	3450.1	3760.3
95% CI (mL^2/min^2)	168.9 to 301.4	562.7 to 935.2	1191.2 to 2659.2	1271.6 to 2153.8	2334.8 to 4565.3	2640.1 to 4880.5
RMSE (mL/min)	15.3	27.4	43.9	41.4	58.7	61.3
95% CI (mL/min)	13.0 to 17.4	23.7 to 30.6	34.5 to 51.6	35.7 to 46.4	48.3 to 67.6	51.4 to 69.9

Abbreviations: ME, mean error; CI, confidence interval; MSE, mean squared error; RMSE, root mean squared error; CL_{SCI}, spinal cord injury equation; CL_M, modified Cockcroft-Gault formula; CL_{24H}, 24-hour endogenous creatinine clearance; CKD-EPI, Long-term Kidney Disease Epidemiology Collaboration equation; CL_{CG}, the Cockcroft-Gault formula; MDRD, the Modification of Diet in Renal Disease equation. Published with permission of Lee [19].

Table 5. Absolute Predictive Performance of Vancomycin Clearance

	ΔME (CI) (mL/min)	ΔMSE (CI) (mL^2/min^2)
CL_{SCI} vs. CL_M	-24.5 (-26.8 TO -22.3)	-513.8 (-709.8 to -317.8)
CL_{SCI} vs. CL_{24H}	-35.5 (-42.6 TO -28.5)	-1690.0 (-2436.5 to -943.5)
CL_{SCI} vs. CKD-EPI	-36.1 (-41.3 TO -30.9)	-1477.5 (-1922.8 to -1032.3)
CL_{SCI} vs. CL_{CG}	-47.5 (-55.9 TO -39.1)	-3214.9 (-4331.1 to -2098.7)
CL_{SCI} vs. MDRD	-50.6 (-59.1 TO -42.1)	-3525.1 (-4645.0 to -2405.2)

Abbreviations: ΔME, the difference in mean errors; ΔMSE, the difference in mean squared errors; CI, confidence interval; $CL_{SCI,}$ spinal cord injury equation; CL_M, modified Cockcroft-Gault formula; CL_{24H}, 24-hour endogenous creatinine clearance; CKD-EPI, Long-term Kidney Disease Epidemiology Collaboration equation; CL_{CG}, the Cockcroft-Gault formula; MDRD, the Modification of Diet in Renal Disease equation. Published with permission of Lee [19].

Table 6. Relative Predictive Performance of Vancomycin Clearance

N = 87	Mean ± S.D. (ml/min)	Difference from patient-specific CL_V (ml/min)	p-value
CL_{SCI}	45.2 ± 9.1	-3.1	0.06
CL_M	69.7 ± 19.7	21.5	< 0.05
CL_{24H}	82.8 ± 36.0	34.6	< 0.05
CKD-EPI	81.2 ± 30.4	33.0	< 0.05
CL_{CG}	92.7 ± 47.0	44.4	< 0.05
MDRD	95.7 ± 45.2	47.5	< 0.05

Abbreviations: CL_V, patient-specific vancomycin clearance ; S.D., standard deviation; $CL_{SCI,}$ spinal cord injury equation; CL_M, modified Cockcroft-Gault formula; CL_{24H}, 24-hour endogenous creatinine clearance; CKD-EPI, Long-term Kidney Disease Epidemiology Collaboration equation; CL_{CG}, the Cockcroft-Gault formula; MDRD, the Modification of Diet in Renal Disease equation. Published with permission of Lee [19].

Table 7. Evaluation of Different Methods to Estimate CL_V

6. Conclusion

SCr determinations are used to estimate the dose of potentially toxic drugs eliminated primarily by the kidneys. Due to immobility and muscle atrophy, individuals with long-duration paraplegia have lower SCr levels relative to their CL_{CR}; this could lead to substantial overestimation of GFR resulting in higher than desired concentrations of medications that increase the risk of toxicity and/or ADRs, especially in persons with existing renal insufficiency. To date, there is no accepted standard method that can reliably predict renal function in paraplegia. Review of the current literature shows that the most widely used CG and MDRD equations overestimate GFR thus not recommended in paraplegia. Although CL_{24H} better predicts renal function compared to CL_{CG} and MDRD in paraplegia, unpracticality of collecting

multiple urine samples as well as the propensity for error from serial collections make this method clinically unfeasible. Different authors have recommended different modification of existing methods. Until more studies become available, the following methods can serve as valuable tools in estimating CL_{DRUG} and renal function in individuals with paraplegia: 0.8 CG, 0.7 MDRD, or CL_{SCI} equations.

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Author details

Jennifer Pai Lee*

Address all correspondence to: jennifer.lee4332a@va.gov

Pharm.D., BCPS, Pharmacy, Veterans Affairs Long Beach Healthcare System, Long Beach, USA

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